Annals of Clinical and Analytical Medicine
Original Research

Evaluation of amplitude-integrated EEG use in the neonatal intensive care unit

Sadrettin Ekmen, Yusuf Deniz
Department of Pediatrics, Faculty of Medicine, Karabuk University, Karabuk, Turkey

Abstract

Aim: Amplitude-integrated electroencephalogram (aEEG) is widely used in neonatal intensive care units (NICU), as it is easier to interpret than conventional EEG and does not prevent invasive procedures in infants. Although it is frequently used in the diagnosis and follow-up of Hypoxic Ischemic Encephalopathy (HIE) and neonatal convulsions developing after perinatal asphyxia, the relationship between neurological examination, aEEG and conventional EEG (cEEG) is still not fully understood.

Material and Methods: This study was carried out by retrospective evaluation of the patient's files and aEEG records of 59 infants who were followed up with aEEG in the Neonatal Intensive Care Unit of Karabuk University Training and Research Hospital between January 1, 2020 and January 31, 2022. One infant who was beyond the neonatal period was not included in the analysis. The data of 38 infants with perinatal asphyxia and 20 infants who were prediagnosed with convulsions were evaluated.

Results: aEEG results of the infants diagnosed with perinatal asphyxia were found to be highly consistent with neurological examination in the early and late periods (84.2%). However, convulsion was detected in aEEG only in 20% of 20 infants with abnormal movements clinically suggestive of convulsions.

Discussion: Our study revealed that the use of aEEG is beneficial in infants who develop HIE after perinatal asphyxia but its benefit in the diagnosis and follow-up of neonatal seizures is not clear. We believe that the use of multi-channel aEEG and/or the use of aEEG together with conventional EEG in neonatal convulsion follow-up will provide more useful information.

Keywords

Hypoxia-Ischemia, Seizures, Newborn, Hypothermia, Electroencephalography

DOI: 10.4328/ACAM.21284 Received: 2022-06-21 Accepted: 2022-07-28 Published Online: 2022-07-29 Printed: 2022-08-01 Ann Clin Anal Med 2022;13(8):942-946
Corresponding Author: Sadrettin Ekmen, Faculty of Medicine, Karabuk University, Karabuk, Turkey.
E-mail: sadrettinekmen@hotmail.com P: +90 505 374 70 80
Corresponding Author ORCID ID: https://orcid.org/0000-0002-9031-6361

Introduction

Amplitude-integrated electroencephalogram (aEEG) has found widespread use in neonatal intensive care units (NICUs) in recent years. The fact that it is easier to interpret than conventional EEG and that it does not prevent invasive procedures in infants are the main reasons why it is preferred by neonatal physicians [1].

There are studies showing that its use is beneficial in many cases such as the diagnosis, follow-up and prognosis prediction of perinatal asphyxia-related hypoxic ischemic encephalopathy (HIE) [2], diagnosis and treatment of subclinical convulsions [3], intraventricular hemorrhage in premature infants [4], prediction of neurological sequelae secondary to hyperbilirubinemia [5,6] and meningitis [7].

However, the main disadvantages are the risks of skipping short-term convulsions due to a compressed time scale and skipping focal seizures due to the use of a small number of electrodes [8].

The Turkish Neonatology Society, in its neonatal encephalopathy guideline, which was updated in 2018, recommended the use of aEEG for diagnosis and follow-up in centers that apply hypothermia treatment [9].

However, the relationship between neurological examination, aEEG and conventional EEG (cEEG) is still not fully understood [10].

Our aim in this study is to evaluate the practical correlation of aEEG with clinical and laboratory results and whether the use of aEEG can help clinicians in the presence of movements suggestive of convulsions in newborns.

Our study was designed in our unit that provides 3rd level neonatal intensive care service at Karabuk University, Faculty of Medicine, Training and Research Hospital. We use the aEEG as a helpful tool, together with clinical and laboratory results, in decision making for hypothermia in infants with hypoxic ischemic encephalopathy (HIE); for the termination of hypothermia treatment until the infant is fully warmed; and to initiate anticonvulsant treatment and evaluate the response to treatment in cases where movements that can be confused with convulsions are observed in newborn infants.

Material and Methods

This study was carried out by retrospective evaluation of patient files and aEEG records of 59 infants who were followed up with aEEG in the Neonatal Intensive Care Unit of Karabuk University Training and Research Hospital between January 1, 2020 and January 31, 2022.

Infants with major congenital malformations who were beyond the neonatal period when aEEG was performed were not included in the study.

Neonatal hypoxic ischemic encephalopathy (HIE) was defined as a clinical syndrome accompanied by neurological findings and acute peripartum-intrapartum event (uterine rupture, cord prolapse, placental abruption, etc.), requiring postnatal neonatal resuscitation, and presenting with metabolic or mixed acidosis in cord blood gas or in blood gas measured within the first 1 hour [9].

The severity of the HIE was assessed using the Modified Sarnat Staging.

aEEG monitoring was performed for the diagnosis and follow-up of infants with stage 2 or stage 3 HIE due to perinatal asphyxia (PNA), after hypothermia and until the end of rewarming (until the infant's rectal temperature rises to 37°C), infants who were candidates for hypothermia but not fully meeting the criteria (HIE Stage 1), and infants with movements thought to be convulsions other than HIE.

DigiTrack Elmiko (made in Poland) was used as the aEEG device. aEEG was evaluated by the relevant neonatal specialist.

aEEG monitoring was evaluated based on amplitude, electrographic seizure, and sleep-wake cycle. Normal amplitude was accepted as >10 μV for the upper limit and >5 μV for the lower limit. Abnormal aEEG was defined as background activity other than continuous normal voltage or immature sleep-wake cycle. Electrographic seizure was defined as an abrupt rise in the minimum amplitude with or without a simultaneous rise in the maximum amplitude, followed by a short period of decreased amplitude, and simultaneous repetitive spikes or sharp waves of at least 5-10 seconds of duration in the aEEG [11-13]

After hypothermia was decided, active hypothermia was applied for 72 hours with a rectal temperature of 33-34°C. Then the rectal temperature was increased to 37°C within 6-12 hours, not exceeding 0.5°C per hour.

When convulsions were detected, phenobarbital was started as the first option in line with the recommendation by The Turkish Neonatology Society. When no response was obtained, phenytoin was added as the second option, and midazolam or levetiracetam treatments were added as the third option [9].

In addition, fluid therapy was limited to 50 cc/kg. Fentanyl infusion was started for pain and a combination of ampicillin and gentamicin was started for infection prophylaxis. Glucose levels, urine output, blood pressure and other vital functions were closely monitored. Specific treatments were started for the detected conditions.

Cord blood gas or arterial blood gas samples were taken within the first 1 hour from all our asphyxic patients.

Our study was approved by the Ethics Committee of Karabuk University, Faculty of Medicine with the decision dated 11/04/2022 and decision number 831. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Data analysis

The SPSS software for Windows® version 26.0 (IBM Corporation, Armonk, New York, United States) was used in the analysis of variables. The data showed a normal distribution, given the Skewness and Kurtosis values of the data remained within the +2.0/-2.0 limit range (George, 2011). Socio-demographic characteristics and mean blood gas values in the study were given as mean and percentage values. For normally distributed values, the Independent Sample Test was used for paired samples, and the one-way ANOVA test was used for samples of two or more. The Mann-Whitney U test was used for paired samples that did not show normal distribution, and the Kruskal-Wallis H test was used in samples of two or more. Pairwise comparison samples were evaluated with the Chi-square test.

Results

The socio-demographic characteristics of the infants included

in our study are presented in Table 1. Initially, 59 infants were included in the study. A patient who was beyond the neonatal period at the time of analysis was excluded. The mean week of delivery was 34.29 ± 2.38 and the mean birth weight was 2970.42 ± 724.387. The mean maternal age of the infants was 27.36 ± 4.80 and the number of pregnancies was 2.41 ± 1.53; 61% were born by cesarean section, 61% were male, and 64.4% were hospitalized with perinatal asphyxia.

Sociodemographic characteristics of the infants diagnosed with perinatal asphyxia are given in Table 2.

Table 1. Socio-demographic characteristics of the infants

Characteristics		Mean ±SD	Min-Max (Median)
Gestational age		34.3 ± 2	30-42 (38)
Birth weigh			900-4700 (3070)
Maternal age		27.3 ± 4	20-40 (27)
Number of pregnancies of the mother			1-7 (2)
		n	%
Type of delivery	C/S	36	61.0
	NSD	23	39.0
Maternal disease	No disease	51	86.4
	Atrial Fibrillation and Flutter	1	1.7
	Diabetes and Preeclampsia	1	1.7
	Diabetes	3	5.1
	Gestational Diabetes	1	1.7
	Gestational HT and Preeclampsia	1	1.7
	Goiter and GDM	1	1.7
Gender of the infant	Male	36	61.0
	Female	23	39.0
Diagnosis for hospitalization of the infant	Perinatal Asphyxia	38	64.4
	Suspected Convulsion	20	33.9
	Asphyxia	1	1.7
Total		59	100

Table 2. Sociodemographic characteristics of the infants diagnosed with perinatal asphyxia

Characteristics		Mean ±SD	Min-Max (Median)
Gestational age		37.5 ± 2	30-40 (38)
Birth weigh		3103.82 ± 661.19	900-4700 (3095)
Maternal age		27.0 ± 4	20-40 (27)
Number of pregnancies of the mother		2.16 ± 1.24	1-5 (2)
		n	%
Type of delivery	C/S	23	60.5
	NSD	15	39.5
Maternal disease	No disease	32	84.2
	Diabetes and Preeclampsia	1	2.6
	Diabetes	3	7.9
	Gestational Diabetes	1	2.6
	Goiter and GDM	1	2.6
Gender of the infant	Male	27	71.1
	Female	11	28.9
Total		38	100

Thirty-eight infants with perinatal asphyxia had an average of 37.58 ± 2.17 weeks of birth and a mean birth weight of 3103.82 ± 661.19. The mean maternal age of the infants was 27.05 ± 4.74 and the number of pregnancies was 2.16 ± 1.24; 60.5% of the infants were born by cesarean section, 71.1% were male, 84.2% had no maternal disease history, and diabetes was the most common maternal disease in those with a maternal disease history.

The aEEG results of the infants diagnosed with perinatal asphyxia are given in Table 3. According to this:

a) Neurological examination and aEEG were found to be highly consistent in the early and late periods (84.2%).

b) Completely inconsistent neurologic examination and aEEG in the early and late periods were detected in only 1 case.

It was observed that the infant who was brought to the emergency room at the age of 2 months due to cardiorespiratory arrest and was diagnosed with postnatal asphyxia had a birth week of 39, a birth weight of 2800 g, a maternal age of 22, and number of maternal pregnancies was 2. It was determined that the delivery type was cesarean section, the gender was male and the mother did not have a chronic disease. When the aEEG characteristics of the baby were examined, aEEG in the first 6 hours was seen to present Burst Suppression, clinical examination in the first 6 hours was seen to present with HIE Stage 3, and aEEG in the 6-24 hours period was seen to present Burst Suppression. It was determined that the clinical examination and aEEG were consistent from the beginning. This patient was not included in the analysis because of being beyond neonatal period.

While convulsion was detected in 20% of the 20 infants with abnormal movements suggesting clinical convulsions in aEEG, 80% of them were evaluated as normal by aEEG.

Table 3. aEEG results of the infants diagnosed with perinatal asphyxia

Characteristics		n	%
aEEG at first 6 hours	Burst Suppression	1	2.6
	Convulsion	3	7.9
	Normal	22	57.9
	Moderately Abnormal	12	31.6
Clinical examination tool (Modified Sarnat Staging)	HIE Stage 1	23	60.5
	HIE Stage 2	15	39.5
aEEG between 6-24 hours	Burst Suppression	1	2.6
	Convulsion	5	13.2
	Normal	26	68.4
	Moderately Abnormal	6	15.8
Consistence of clinical examination and aEEG	Consistent in the early period, inconsistent in the late period	2	5.3
	Inconsistent in the early period, consistent in the late period	3	7.9
	Completely consistent in the early and late periods	32	84.2
	Completely inconsistent in the early and late periods	1	2.6
	Convulsion confirmed	2	5.3
	Convulsion not confirmed	3	7.9
Total		38	100

Early: First 6 hours of life; Late: Period after the first 6 hours of life

Discussion

The definition of HIE severity remains a subject of debate, and there is no clear consensus in the literature about mild, moderate, and severe injury-staging definitions [14]. The original 1976 American PMID (987769) report, in which HIE staging was first introduced, led to modification and different versions of the Sarnat examination. Therapeutic hypothermia (TH) has an extremely critical importance in children who need TH treatment. According to the results of Cochrane meta-analysis evaluating TH studies, it was determined that TH reduces neurodevelopmental disability and mortality after 18 months [15].

Today, in addition to the severity of HIE, aEEG is one of the more common methods by which clinicians try to estimate the severity of brain damage in the first few hours or days of life [16]. However, the relationship between neurological examination, aEEG and conventional EEG (cEEG) is still not fully understood [10]. In order to apply the critically important TH treatment to the patients in need, it is necessary to correctly stage the severity of encephalopathy and to determine the best method for staging.

Neonatal seizures are the most common neurological emergency in the neonatal period and frequently pose diagnostic and management challenges for clinicians worldwide [17].

In our study, a high level of consistency was found between aEEG and neurological findings in infants diagnosed with HIE (84.2%), but the rate of evaluation of abnormal movements suggesting clinical convulsions as convulsions was only 20% with aEEG. We think that this is related to the facts that aEEG skips short and focal convulsions, the sensitivity of aEEG is low due to the use of single-channel aEEG, and the fact that most cases that are considered as convulsions in the neonatal period are actually not convulsions when evaluated electrographically.

In a study by Massaro et al. in which they reviewed the aEEG data of 75 encephalopathic newborns to predict the short-term outcomes of infants with HIE, they reported that the detection of an abnormal aEEG background predicted a negative outcome during the course of hypothermia [18]. The results of this study support our findings.

Similar to the study by Vegda H. et al., our results suggest that aEEG has a low success rate in demonstrating neonatal convulsions. As they stated, this result suggests that aEEG often misses short seizures (<30 sec) or low-amplitude seizures. There is also a risk of misinterpretation of artifacts as seizures, and therefore the annotation should be appropriately noted [19].

Moreover, the American Society of Clinical Neurophysiology recommends 24-hour EEG monitoring rather than aEEG in all newborns at high risk for seizures, such as newborns with acute brain injury, clinical encephalopathy, or abnormal paroxysmal events [20].

According to the results of a meta-analysis evaluating aEEG in the diagnosis and treatment of seizures in 2015, which supports the results of our study, it has been reported that aEEG has relatively low sensitivity and specificity for the diagnosis of neonatal seizures, and therefore, aEEG is not suitable for the diagnosis and treatment of neonatal seizures [21].

Today, the accuracy of aEEG is still not fully determined. Different results continue to be shown in different studies. In a recent systematic meta-analysis, results were obtained showing that the sensitivity of aEEG varies significantly and the seizure detection rate is lower than that of cEEG [22]. In another study, Shankaran et al. reported that aEEG background pattern did not significantly increase the value of encephalopathy stage at study entry in predicting death and disability in infants with HIE [23]. In our study, an abnormal aEEG pattern was detected in only one (2.6%) of the newborns with Stage 1 encephalopathy scores, which would not typically be considered for TH.

In another recent study [24], in line with our results, the inter-rater reliability of aEEG for detecting neonatal seizures was "moderate", the inter-rater reliability of aEEG for detecting seizure duration was "weak", and aEEG has been shown to be unsuccessful to detect multiple seizures and underestimate the duration of the seizure.

In addition, there are studies in the literature reporting that the use of multi-channel aEEG has a better sensitivity to detect seizures than single-channel aEEG [25].

Therefore, it should be noted that one of the reasons for the low seizure detection rate in our study may be due to the use of a single channel aEEG.

As emphasized by Herzberg et al [10], we suggest using aEEG as an additional modality to neurological examination in the diagnosis and treatment of HIE, since it allows a more accurate assessment of the severity of encephalopathy when combined with neurological examination.

Conclusion: Our study revealed that the use of aEEG in infants developing HIE in perinatal asphyxia is beneficial but its benefit in the diagnosis and follow-up of neonatal seizures is not clear. We believe that the use of multi-channel aEEG and/or its use together with conventional EEG in neonatal seizure follow-up will provide more useful information.

The limitations of our study: The small sample size due to its single-center design, the use of single-channel aEEG, the lack of simultaneous cEEG monitoring, the inability to compare with neuroimaging, and the failure to evaluate its effect in predicting long-term neurodevelopment can be counted as limitations of our study.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Chen C, Sun C, Leonhardt S, Andriessen P, Niemarkt H, Chen W. Amplitude-integrated electroencephalography applications and algorithms in neonates: A systematic review. IEEE Access. 2019; 7:141766-781.

2. Ahearne CE, Boylan GB, Murray DM. Short and long term prognosis in perinatal asphyxia: An update. World J Clin Pediatr. 2016; 5(1): 67-74.

3. van Rooij LG, Toet MC, van Huffelen AC, Groenendaal F, Laan W, Zecic A, et

al. Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized, controlled trial. Pediatrics. 2010;125(2):e358-66.
4. Schreiner C, Hammerl M, Neubauer V, Kiechl-Kohlendorfer U, Griesmaier E. Amplitude-integrated electroencephalography signals in preterm infants with cerebral hemorrhage. Early Hum Dev. 2021; 154:105309.
5. Yuan X, Song J, Gao L, Cheng Y, Dong H, Zhang R, et al. Early amplitude-integrated electroencephalography predicts long-term outcomes in term and near-term Newborns with Severe Hyperbilirubinemia. Pediatr Neurol. 2019 Sep;98:68-73.
6. Chang H, Zheng J, Ju J, Huang S, Yang X, Tian R, et al. Amplitude-integrated electroencephalography improves the predictive ability of acute bilirubin encephalopathy. Transl Pediatr. 2021;10(3):647-56.
7. ter Horst HJ, van Olffen M, Remmelts HJ, de Vries H, Bos AF. The prognostic value of amplitude integrated EEG in neonatal sepsis and/or meningitis. Acta Paediatr. 2010;99(2):194-200.
8. Shellhaas RA, Soaita AI, Clancy RR. Sensitivity of amplitude- integrated electroencephalography for neonatal seizure detection. Pediatrics. 2007; 120(4):770-7.
9. Akisu M, Kumral A, Canpolat FE. Turkish neonatal society guideline on neonatal encephalopathy. Turkish Archives of Pediatrics. 2018; 53(Suppl.1):S32.
10. Herzberg EM, Landers J, Greco KF, Feldman HA, Sansevere AJ, Soul JS. Improving the diagnosis of neonatal encephalopathy: validation of a novel encephalopathy scale for hypoxic-ischemic encephalopathy (HIE) using electroencephalogram (EEG). Pediatrics. 2021; 147(3):711-12.
11. Hellström-Westas L, Rosén I. Continuous brain-function monitoring: state of the art in clinical practice. Semin Fetal Neonatal Med. 2006;11:503–11.
12. al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. Pediatrics. 1999;103(6 Pt 1):1263–71.
13. Yuan X, Kang W, Song J, Guo J, Guo L, Zhang R, et al. Prognostic value of amplitude- integrated EEG in neonates with high risk of neurological sequelae. Ann Clin Transl Neurol. 2020; 7(2):210-18.
14. Peeples ES, Rao R, Dizon MLV, Johnson YR, Joe P, Flibotte J, et al. Predictive models of neurodevelopmental outcomes after neonatal hypoxic-ischemic encephalopathy. Pediatrics. 2021;147(2):e2020022962.
15. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013; 2013(1):CD003311.
16. Liu W, Yang Q, Wei H, Dong W, Fan Y, Hua Z. Prognostic Value of Clinical Tests in Neonates With Hypoxic-Ischemic Encephalopathy Treated with Therapeutic Hypothermia: A Systematic Review and Meta-Analysis. Front Neurol. 2020;11:133.
17. Abend NS, Jensen FE, Inder T.E, Volpe J.J. Neonatal seizures. In: Volpe J.J, Inder T.E, Darras B.T, de Vries L.S, du Plessis A.J, Neil J.J, editors. Volpe's neurology of the newborn. Philadelphia: Elsevier; 2018. p. 275–321.
18. Massaro AN, Tsuchida T, Kadom N, El-Dib M, Glass P, Baumgart S, et al. aEEG evolution during therapeutic hypothermia and prediction of NICU outcome in encephalopathic neonates. Neonatology. 2012;102(3):197-202.
19. Vegda H, Krishnan V, Variane G, Bagayi V, Ivain P, Pressler RM. Neonatal Seizures- Perspective in Low-and Middle-Income Countries. Indian J Pediatr. 2022; 89(3):245-53.
20. Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, et al. The American Clinical Neurophysiology Society's Guideline on Continuous Electroencephalography Monitoring in Neonates. J Clin Neurophysiol. 2011;28(6):611-7.
21. Rakshasbhuvankar A, Paul S, Nagarajan L, Ghosh S, Rao S. Amplitude-integrated EEG for detection of neonatal seizures: a systematic review. Seizure. 2015; 33:90-8.
22. Falsaperla R, Scalia B, Giaccone F, Suppiej A, Pulvirenti A, Mailo J, et al. aEEG vs cEEG's sensivity for seizure detection in the setting of neonatal intensive care units: A systematic review and meta-analysis. Acta Paediatr. 2022;111(5):916-26.
23. Shankaran S, Pappas A, McDonald SA, Laptook AR, Bara R, Ehrenkranz RA, et al. Predictive value of an early amplitude integrated electroencephalogram and neurologic examination. Pediatrics. 2011;128(1):e112-20.
24. Rakshasbhuvankar AA, Wagh D, Athikarisamy SE, Davis J, Nathan EA, Palumbo L, et al. Inter-rater reliability of amplitude-integrated EEG for the detection of neonatal seizures. Early Hum Dev. 2020; 143:105011.
25. Zhang L, Zhou YX, Chang LW, Luo XP. Diagnostic value of amplitude-integrated electroencephalogram in neonatal seizures. Neurosci Bull. 2011; 27(4):251-7.

How to cite this article:
Sadrettin Ekmen, Yusuf Deniz. *Evaluation of amplitude-integrated EEG use in the neonatal intensive care unit. Ann Clin Anal Med 2022;13(8):942-946*